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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,633	11/20/2006	Salvatore Avolio	ITT0061P	2568

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EXAMINER	
LOEWE, SUN JAE Y	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
03/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,633	AVOLIO ET AL.	
	Examiner	Art Unit	
	SUN JAE Y. LOEWE	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-19* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,13 and 14* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-7-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10, 13, 14 and 15-19 are pending in the instant application. Claims 11 and 12 were cancelled by preliminary amendment filed on April 7, 2006.

Election/Restrictions

2. Applicant's election with traverse of Group I, and species of example 11 " 3-cyclohexyl-1-(3,5-dibromobenzyl)-2-phenyl-1*H*-indole-6-carboxylic acid", in the reply filed on November January 11, 2008 is acknowledged.

The traversal is on the ground(s):

" It is respectfully submitted that search and examination of the entire application could be made without serious burden. *See* MPEP §803"

The instant application is a national stage entry of PCT/GB2004/004306 and thus the criteria of burden (MPEP 800, for national applications filed under 35 USC 111) does not apply.

The arguments are not found persuasive for the reason above. The restriction requirement is still deemed proper and is therefore made FINAL.

3. The following guidelines are provided by MPEP 1893.03(d):

" Note: the determination regarding unity of inven-

> tion is made without regard to whether a group of inventions is claimed in separate claims or as alternatives within a single claim. The basic criteria for unity of invention are the same, regardless of the manner in which applicant chooses to draft a claim or claims.
>
> If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any non-
>
> ¶ *18.20 National Stage Election of Species in 35 U.S.C. 371 Applications*
>
> Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If ,,

The generic claims were not allowable (Sections 9-11). Pursuant MPEP 1893.03(d), non-elected species were withdrawn from further consideration. The search was limited to the elected species.

4. Claims 15-19 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter. Applicant timely traversed the restriction (election) requirement in the reply filed on January 11, 2008.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on April 7, 2006 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is enclosed herewith.

Claim Objections

7. Claims 1-10, 13 and 14 objected to for containing non-elected subject matter.

8. Claim 10 objected to because of the following informality: the claim is not written in proper Markush format (MPEP 803.02). The following correction is suggested: insert the term "and" between

1-benzyl-3-cyclohexyl-2-(3-{[isopropyl(methyl)amino]-methyl}phenyl)-1*H*-indole-6-carboxylic acid, and

3-cyclohexyl-1-({5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}methyl)-2-phenyl-1-1*H*-indole-6-carboxylic acid,

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 14 rejected under 35 USC 112 first paragraph as failing to comply with the written description requirement.

The guidelines provided in MPEP 2163.II. were used to determine compliance with the written description requirement.

1. **For Each Claim, Determine What the Claim as a Whole Covers**

Claims drawn to pharmaceutical compositions
"which further comprises one or more other agents for the treatment of viral infections."

2. **Review the Entire Application to Understand How Applicant Provides Support for the Claimed Invention Including Each Element and/or Step**

The specification does provide support for the ingredients noted above (see below).

3. **Determine Whether There is Sufficient Written Description to Inform a Skilled Artisan That Applicant was in Possession of the Claimed Invention as a Whole at the Time the Application Was Filed**

MPEP 2163.II.3 states that possession may be shown by the following:

> Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.

In the instant case, the claimed pharmaceutical composition was not reduced to practice. The additional ingredients noted in section 1 were neither described by examples, structural/chemical formulas, references. As stated in section 2, the specification does not provide support for these ingredients.

In view of this analysis, it is determined that the claims *prima facie* lack written description.

10. Claims 1-9, 13 and 14 rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient

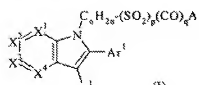
variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. Scope of Claims (based on a subgenus of compounds within elected Group I)

Compounds of Formula I with the following structural limitations:

X1=CRa; X2=CR1; X3=CR2; X4=CRb; A1=cyclohexyl; one of R1 or R2 is carboxy; Ar1=Ar=phenyl.



(I)

The following variables are claimed *broader* than what is supported by the disclosure (see below section II):

R^1 & R^2:	for all claims *except* claims 2 and 9
R^a:	for all claims *except* claims 2 and 9

R^b:	for all claims *except* claims 3 and 9
Q^1 & Q^2:	for all claims
Q^3:	for all claims *except* claim 9
Q^4:	for all claims

II. Scope of Disclosure

Reduction to Practice:

The compounds reduced to practice support the following definitions for the variables

R^1, R^2, R^a, R^b:	hydrogen, C_{1-4}alkyl
Q^1 - Q^3:	hydroxy, fluorine, chlorine, bromine or iodine atom or a C_{1-6}alkyl, C_{1-6}alkyl substituted by not more than 5 fluorine atoms, C_{1-6}alkoxyl, C_{1-6}alkoxyl substituted by not more than 5 fluorine atoms.
Q^4:	fluorine, chlorine, bromine or iodine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxy or difluoromethoxy group,

Reduction to Structural or Chemical Formulas:

There is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

A structure-activity study (SAR) that address the activity of a subgenus of the instantly claimed compounds as a function of structural modifications. These studies show that structural modifications influence the ability of the disclosed compounds to inhibit HCV polymerase. It is not disclosed in the instant specification what *specific structural elements* would allow for preservation of activity within the broader genus claimed.

III. Analysis of Fulfillment of Written Description Requirement:

In the absence of a correlation between structure and function, it is not possible to know what modifications to the instantly claimed core structure will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1-9, 13 and 14; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(Enablement)

11. Claims 1-9, 13 and 14 rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for making and using compounds that have adequate written description. The specification is not enabling for using compounds that are not supported by the disclosure, as the only utility disclosed is that for the inhibition of HCV polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that

a disclosure does not satisfy the enablement requirement and whether any necessary

experimentation is undue". The factors are applied below to the instant claims.

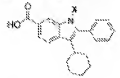
The breadth of the claims
Claims drawn to compounds that *do not* have written description support.

The nature of the invention
The compounds are disclosed to be inhibitors of HCV polymerase. Additional utility is neither disclosed nor known in the art.

The state of the prior art/level of ordinary skill/level of predictability
The level of ordinary skill is high, but the level of predictability in the art is low. The activity of a compound towards an enzyme or receptor depends on the interaction between the chemical groups/moieties of the compound with specific residues in the binding pocket of the protein/receptor. It is well documented in the art that changes to the structure/chemical properties of a compound can have unpredictable results on its overall binding and/or functional binding ability. Studies suggest that this is the case with the HCV polymerase enzyme, note illustrative example below:

- Harper et al., for example, see below

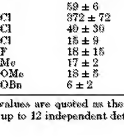
Table 1. NS5B Enzyme Inhibition (IC_{50}) and Cell-Based Efficacy (EC_{50}) for N-Substituted Indole Inhibitors



compd	X	IC_{50} (nM)[a]	EC_{50} (μM)[a]
7	H	48 ± 9	6.7 ± 0.5
8	Me	28 ± 8	6.0 ± 0.5
9	$-CH_2Ph$	37 ± 3	14.2 ± 0.5
10	$-SO_2Ph$	485 ± 180	>50
11	$-CH_2C(O)NHSO_2Me$	42[b]	>50
12	$-CH_2CH_2$-morpholine	111 ± 55	4.6 ± 1.4
13	$-CH_2C(O)NMe_2$	59 ± 6	1.5 ± 0.6
14	$-CH_2C(O)$-morpholine	26 ± 11	9.8 ± 0.3

[a] IC_{50} and EC_{50} values are quoted as the arithmetic mean ± standard deviation for up to 12 independent determinations. [b] $n = 1$.

Table 2. SAR at the C2 Position of 13: Intrinsic Potency and Cell-Based Activity



compd	R	IC_{50} (nM)[a]	EC_{50} (μM)[a]
13	H	59 ± 6	1.5 ± 0.6
15	2-Cl	372 ± 72	nd[b]
16	3-Cl	40 ± 30	4.5 ± 0.5
17	4-Cl	15 ± 9	0.9 ± 0.3
18	3-F	18 ± 15	0.8 ± 0.1
19	4-Me	17 ± 2	0.5 ± 0.2
20	4-OMe	18 ± 5	0.5 ± 0.1
21	4-OBn	6 ± 2	2.6 ± 0.6

[a] IC_{50} and EC_{50} values are quoted as the arithmetic mean ± standard deviation up to 12 independent determinations. [b] nd = not determined.

The example above is provided to illustrate inability, absent structural correlation studies, to predict inhibitory activity as a function of changing the variables to the core structure.

It is not known what specific structural changes are tolerated for producing active HCV polymerase inhibitors. One of ordinary skill could not predict which of the structurally diverse compounds, embraced by the claims but not exemplified/supported by the disclosure, would possess the desired activity. Lacking use as HCV polymerase inhibitors, in view of the absence of an alternate utility, one of ordinary skill is not enabled by the disclosure to use the compounds which do not have written description support.

The amount of direction provided by the inventor/existence of working examples

Direction and working examples limited to the compounds that are adequately represented by the disclosure (Section 10.II)

The quantity of experimentation needed to make or use the invention
It would require undue experimentation for one of ordinary skill to first test which of the compounds possess this activity before being able to practice the invention commensurate in scope with the breadth of the instant claims.

Conclusion

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SL
2-22-2008

/Kamal Saeed, Ph.D./
Primary Examiner
Art Unit 1626